REMARKS

Applicants respectfully request amendment to the specification. Applicants hereby state that the proposed amendments do not constitute new matter. The amendments are made to correct obvious typographical errors or to delete certain subject matter.

Claims 106, 110, 111, 112, 114 and 115 are amended herein. Support for the amendment to claim 106 may at least be found at page 31, lines 25-26, page 32, line 1, and page 33, lines 1-4, of the specification. Support for the amendment to claim 115 may be found at least at page 11, lines 7-23, page 12, lines 17-20, and page 30, lines 10-16, of the specification. Claims 110, 111, 112 and 114 have been amended, by deleting the word "factor" solely for purposes of clarity and the amendments are not related to patentability. "Therefore *Festo* is not applicable." *Turbocare Division of DemagDelaval Turbomachinery Corp. v. General Electric Co.*, 60 U.S.P.Q.2d 1017 (Fed. Cir. 2001) (holding that because a newly added claim only redefined the small clearance position limitation without narrowing the claim" *Festo* was not applicable.) One of ordinary skill in the art appreciates that factors, such as tumor necrosis factor, are also proteins.

The drawings accompanying this application were objected to for minor informalities. Corrected drawings are being filed simultaneously with this response.

REJECTION OF CLAIMS 106-142 UNDER 35 U.S.C. §112, FIRST PARAGRAPH:

The Office Action of July 19, 2001 alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate with the scope of the claims. The Examiner contends that the specification does not provide an enabling disclosure for 1) an immunosuppressive agent or combination of agents capable of rendering a recipient animal tolerant to xenogeneic or allogeneic tissue or provide sufficient guidance as to the level of immunodeficiency necessary to allow xenogeneic or allogeneic cells to express therapeutic levels of any gene for a period of time sufficient to achieve any therapeutic effect on any disease or condition and 2) the delivery of any type of transfected cell to any other cellular location using any method of delivery resulting in the expression of therapeutic levels of protein or the treatment of any disease or

condition. The Examiner further contends that the limited guidance provided by the specification, combined with the unpredictability in the art, leads to the requirement of undue experimentation to practice the invention.

The presently claimed invention relates to the treatment of diseases by the site-specific instillation or transformation of cells. The inventors have found that transfecting a vascular cell *ex vivo* and then transplanting it is an effective way to treat various diseases and genetic disorders. The present claims are directed to a method of introducing a therapeutic protein in a mammal by delivering a transfected vascular cell to the blood vessel of the mammal in a site-specific manner. The present claims are also directed to a method of treating a human patient by site-specifically instilling vascular cells, such as endothelial, smooth muscle, or parenchymal cells, capable of secreting a therapeutic protein or factor, into the blood vessel of a human patient.

The Examiner's first rejection is based on the Examiner's belief that the specification does not enable one to render the recipient animal tolerant to xenogeneic or allogeneic tissue or provide sufficient guidance as to the level of immunodeficiency necessary to allow xenogeneic or allogeneic cells to express therapeutic levels of any gene for a period of time sufficient to achieve any therapeutic effect on any disease or condition. The specification provides ample description to enable one of skill in the art to make or use the present invention, specifically how to avoid illiciting a host immune response, while still allowing cells to express therapeutic levels of a gene product for a period of time sufficient to achieve a therapeutic effect for a disease or condition commensurate with the scope of the claims.

Applicants have amended the claims to reflect that the cells utilized in the approaches mentioned above and described more fully below, are syngeneic to the cells of the recipient or patient.

More specifically, Applicants disclose, at least at page 30 of the specification and at page 4 of the Amendment, that cell-mediated gene transfer can avoid host immune response by transferring genetic material into cells derived from the host and then, after this modification, reintroducing these cells into the host.

Further, one of ordinary skill in the art, at the time of the invention, would appreciate how to avoid a host immune response. For example, at the time of invention, it was known in the art that azathioprine, corticosteroids, cyclosporine, and polyclonal and monoclonal antibodies

could be used in combination or alone to achieve suppression of the immune system. (Lazarovits, A.I. The Therapy of Rejection. *Clin Invest Med* 1989 Oct;12(5):311-5).

The specification provides ample description to enable one of skill in the art to make or use the present invention, specifically how to deliver a transfected cell to another cellular location, using one of the claimed methods of delivery resulting in the expression of therapeutic levels of protein for the treatment of a disease or condition, commensurate with the scope of the claims.

For example both Figures 1 and 2 illustrate how a catheter (e.g., as disclosed in U.S. Patent 4,636,195) may be used to locally introduce transformed vascular cells. Further, at the bottom of page 9 of the specification, Applicants disclose that "[i]n the case of delivery to an organ, the catheter may be introduced into the major artery supplying the tissue. Cells containing recombinant genes or vectors can be introduced through a central instillation port after temporary occlusion of the arterial circulation. In this way, cells or vector DNA may be delivered to a large amount of parenchymal tissue distributed through the capillary circulation..." For further example, pages 14-20 discuss the introduction of cells expressing normal or exogenous proteins into the vasculature. Still further, pages 28-30 describe kits that may be used to achieve instillation of cells, capable of secreting a therapeutic protein or factor, into the vasculature of a mammal. Even more specifically, pages 31-36 demonstrate the feasibility and procedure for transfer of endothelial cells and gene transplantation. One of ordinary skill in the art, in light of these disclosures, would appreciate that therapeutic proteins, such as those disclosed at page 27 of the specification, could be used to produce a detectable therapeutic effect for a disease or condition. For example, page 27 of the specification further suggests that the skilled artisan use genetic material coding for tPA or modifications thereof, along with urokinase to transform cells in treating ischemic diseases or thrombotic diseases.

Still further, as the Examiner points out, the examples in this application demonstrate the successful transfection of endothelial cells with a vector encoding lacZ, and the instillation of these cells by a balloon catheter to blood vessels *in vivo*. Further, the examples demonstrate that the transplanted endothelial cells expressed detectable levels of β – galactosidase following transplantation for approximately six weeks. Also, as mentioned above, at page 27 of the specification, Applicants teach that this invention may be used to treat ischemic diseases (thrombotic diseases) by transfecting vascular cells with genetic material coding for tissue

plasminogen activator (tPA) or modifications thereof. Still further, at page 27 of the specification, Applicants teach that ischemic organ failure may be treated, using the present invention, by transfecting vascular cells with genetic material coding for recollateralization agents, such as transforming growth factor α (TGF-α), transforming growth factor – β (TGF-β), angiogenin, tumor necrosis factor α, tumor necrosis factor β, acidic fibroblast growth factor or basic fibroblast growth factor. One of ordinary skill in the art would appreciate, based on the success of expression of transfected cells demonstrated in the examples, that the expression of other genetic material, such as tPA, could be achieved using the same techniques. Further the skilled artisan would appreciate that the presence of a therapeutic protein in the vicinity of where such a protein might have its therapeutic effect, would result in treatment of the disease or condition caused or exacerbated by lack of that therapeutic protein.

Whether an invention is enabled is to be judged according to what the ordinary skilled artisan, at the time the invention is made, would be able to do, based on the description set forth in the patent application. *In re Wright,* 999 F.2d 1557, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993). The paragraphs and disclosures highlighted above show that Applicant's description of their invention was sufficient to enable the ordinary skilled artisan to practice the invention commensurate with the scope of the claims

Undue experimentation would **not** be required to practice the invention as claimed. The specification describes several approaches for the *ex vivo* transfection of a vascular cell, followed by transplantation of that cell. Applicants appreciate that certain conditions may be varied greatly and still remain within the scope of the invention. However, the specification guides the person of skill in the art on how to determine if the conditions they are using are effective. While some experimentation may be required when using different transfection vectors, for example, this experimentation cannot be considered undue. Thus one of skill in the art, using the specification as a guide, would be able to practice the invention with out the need for undue experimentation. Therefore, Applicants respectfully request that the rejection of claims 106-142 under 35 U.S.C. §112, first paragraph, be withdrawn.

REJECTION OF CLAIM 120 UNDER 35 U.S.C. §112, SECOND PARAGRAPH:

The Examiner has rejected claim 120 as being indefinite. Applicants submit that the present claims satisfy the requirements of 35 U.S.C. § 112, second paragraph. The purpose of the claims is not to "describe" the invention. *Orthokinetics v. Safety Travel Chairs,* 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). A claim is valid if one of skill in the art would understand what is claimed when the claim is read in light of the specification. *Id.* The present invention relates to the treatment of diseases by the site-specific instillation or transformation of cells and kits therefor. As discussed in the specification, at page 30, "the (exogenous) protein treats the disease or may be useful for diagnostic purposes". Further, as discussed at page 31 of the specification, "[t]he present method may also use exogenous proteins of diagnostic value. For example, a marker protein, such as β-galactosidase, may be used to monitor cell migration."

Claim 120 recites that the protein produced by the instilled cells has a diagnostic effect. When this claim is read in light of the specification, more specifically in light of the disclosures highlighted above, it is clear that by "diagnostic effect" the Applicants meant that the expression of the protein itself would be "diagnostic" for some condition or disease.

The Examiner has rejected claim 120 as being indefinite. Applicants submit that the present claims apprise the skilled practitioner of the metes and bounds of the claimed subject matter and satisfy the requirements of 35 U.S.C. § 112, second paragraph. Thus Applicants respectfully request that the rejection of the claims 120 under this section be withdrawn.

REJECTION OF CLAIMS 106, 109-111, 113-121, 123-124, AND 131-134 UNDER 35 U.S.C. §102(e):

Applicants have amended the claims to clarify that the present invention is directed to the transformation of vascular cells. Vascular cell types do not include CNS or fibroblast cells. Therefore, as amended, the claims do not embrace CNS cells or fibroblast cells.

The Examiner has cited the Gage patent (U.S. Patent No. 5,762,926) as describing the invention of Applicants. As the Examiner states, the Gage patent describes the implantation of transfected fibroblasts, or other CNS cells, by surgery or injection.

The Gage patent does not describe or teach all elements of the amended claims of Applicants' invention. For example, the Gage patent, at least, does not disclose the implantation of vascular cell types, but instead describes the implantation of fibroblasts and CNS cell types. Therefore, Gage does not anticipate Applicants' invention. Further, it would not be obvious to the skilled artisan that techniques for introducing fibroblasts, cells present in an unassociated form in the blood, would also work to introduce vascular cells, which form the various layers of the blood vessel wall, rather than travel freely in bodily fluids. For example, fibroblasts, unlike vascular cells, are commonly associated with the connective tissues (other cells of the connective tissue include macrophages, histiocytes, mast cells, plasma cells, neutrophils, eodinophils, myofibroblasts, and undifferentiated mesenchymal cells) and are actively produced in response to wounding. (Ross, M.H., Edward J. Reith, *Histology, A Text and Atlas*, Harper & Row 1985).

Thus, Applicants respectfully submit that their present invention can be distinguished from the invention described in the Gage patent, in that the claims have been amended to clarify that Applicants' invention is directed to the transformation of vascular cells, whereas the Gage patent describes the transformation of central nervous system cells generally and fibroblasts more specifically. Therefore, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 102(e) be withdrawn.

CONCLUSION

In view of the arguments above, Applicants respectfully submit that all of the pending claims are in condition for allowance and seek an early allowance thereof. If for any reason, the Examiner is unable to allow the application in the next Office Action and believes that an interview would be helpful to resolve any remaining issues, she is respectfully requested to contact the undersigned attorney at (312) 321-4283.

Respectfully submitted,

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